Directed Stem Cell Differentiation for Cell-Based Therapies for Heart, Lung, and Blood Diseases

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The official link for this solicitation is: http://grants.nih.gov/grants/guide/pa-files/PA-09-250.html

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Description:

The purpose of this Funding Opportunity Announcement (FOA) is to define the factors and mechanisms controlling the differentiation of embryonic or adult stem or progenitor cells, either *in vitro* or *in vivo*. The FOA is designed to stimulate new scientific advances in stem cell differentiation including technology research that may not be hypothesis driven. The long range goal of this program is the development of methods to direct the differentiation or development of stem cells along specific cell lineages to yield replacement cells for clinical use, whether the replacement cells are formed *in vitro* for delivery or formed *in vivo* in the tissue or organ environment.

Basic research has identified stem cells or progenitor cells with potential applications for the repair or regeneration of heart, blood vessels, lung, and blood tissues. However, in order to utilize these stem or progenitor cells for reparative or regenerative therapeutic strategies, it will be necessary to differentiate and expand these cells into specific cell lineages and in sufficient quantities. Cells suitable for cell based therapy need to (1) provide robust and persistent engraftment to repair injury or correct genetic disease; (2) undergo tissue specific differentiation, either prior to transplantation or *in vivo;* and (3) be expandable to the scale required for clinical application. Safety considerations are paramount, including a lack of tumor formation and the prevention of germ line transmission. Stem cell differentiation likely involves critical pairings of cell types essential to lineage specification. Therefore, the influence of resident cells on the stem cell in the microenvironment of the niche must

be assessed.

Our understanding of stem cell differentiation and development has been limited by the complexity of the biology. Prior research on individual growth factors, signaling molecules, or extracellular matrix components has been insufficient to define the factors and conditions required for the production of differentiated cells in sufficient number for clinical use or to stimulate appropriate differentiation in situ. Advances in stem cell biology, including the identification of key molecules regulating self-renewal and differentiation and the establishment of new model systems, provide opportunities to address this roadblock and to stimulate the field.

Critical elements that control the proliferation versus differentiation choices of resident heart, vascular, lung, and blood stem or progenitor cells need to be understood. This information is of paramount importance to devising and successfully implementing cell-based therapies for heart, vascular, lung, and blood diseases. Cell-based therapies could impact treatment of diseases such as myocardial infarction, heart failure, end-stage emphysema, and the repair of atherosclerotic vessels. The availability of lineage-specific blood cells could lead to novel replenishment therapies including the establishment of either immune competence or immune tolerance.

This announcement focuses on elucidating and defining factors that direct cell differentiation of stem or progenitor cells, of embryonic or adult origin, into defined pathways or cell lineages and maintaining that differentiated state. Knowledge of these factors should provide us with the ability to differentiate and expand stem and progenitor cells into the required cell lineages and in the quantities required for cell-based therapies so that promising advances can be applied clinically.

Research Topics

Research topics are intended to provide a perspective on the scope of research that would meet the objectives of this program. It is not required that all or any of these topics be included. Applicants are encouraged to consider other topics that are relevant to the goals of this FOA. Examples of research topics include but are not limited to those listed below:

- Identify and characterize lung or heart stem or progenitor cells and establish lineage of specific heart and lung cell types.
- Define vascular progenitor cells and assess their potential for vascular differentiation.
- Determine methods and conditions to differentiate blood stem cells into platelets, red cells, T cells or other blood products for transfusion medicine and other applications.
- Define the factors and mechanisms that control the differentiation of stem or progenitor cell into specific cell subtypes.
- Define conditions for expansion of stem or progenitor cells *in vitro* and *in vivo* into defined lineages for use in biologic, pharmacologic, tissue engineering, gene transfer, or other protocols.
- Elucidate the influence of the stem cell niche or microenvironment on stem cell self-renewal and differentiation.
- Assess the role of accessory cells, e.g., mesenchymal or stromal cells, and their potential to form differentiated cells.
- Investigate the use of novel stem cell factors, e.g., Wnt pathway, hoxB4 and homologues, and notch pathway, for cell expansion and differentiation;
- Develop methodologies to isolate, characterize, and purify differentiated cell lineages.
- Investigate the potential for tumor formation, germ line transmission or other safety issues.
- Assess the role of stem cell donor age, gender, risk factors, or disease status on differentiation and function of cells derived.